Prevalence of hemangiosarcoma in anemic dogs with a splenic mass and hemoperitoneum requiring a transfusion: 71 cases (2003–2005)

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Objective—To determine prevalence of splenic hemangiosarcoma in anemic dogs with a splenic mass and hemoperitoneum requiring a transfusion and to identify factors that could differentiate between dogs with hemangiosarcoma and dogs with other splenic masses at the time of hospital admission.

Design—Retrospective case series.

Animals—71 dogs.

Procedures—Medical records, blood bank logs, and histologic reports of dogs with a splenic mass and hemoperitoneum that required a transfusion between 2003 and 2005 were reviewed. Dogs that received a transfusion of packed RBCs, were splenectomized, and had a definitive histologic diagnosis were included.

Results—Signalment of dogs was similar to that in other reports. Malignant splenic neoplasia was identified in 54 of 71 (76.1%) dogs, whereas 17 of 71 (23.9%) dogs had a benign splenic lesion. Of 54 dogs with malignant splenic neoplasia, 50 (92.6% [70.4% of all dogs]) had splenic hemangiosarcoma. In addition, dogs with splenic hemangiosarcoma had significantly lower total solids (TS) concentrations and platelet counts at admission. Finally, hemoperitoneum was strongly associated with a diagnosis of splenic hemangiosarcoma.

Conclusions and Clinical Relevance—In this clinical population of dogs, prevalence of hemangiosarcoma was higher than in other studies. Dogs with hemangiosarcoma in this study had significantly lower TS concentrations and platelet counts at the time of admission, compared with values for dogs with other splenic masses. No other markers were useful in differentiating dogs with hemangiosarcoma. It is important to discuss the prevalence of and poor prognosis associated with hemangiosarcoma with owners when they are contemplating whether to proceed with treatment. (J Am Vet Med Assoc 2008;232:553–558)

Hemangiosarcoma is a malignant neoplasm of vascular endothelial origin. It is reported in approximately 0.3% to 2% of recorded necropsies and represents approximately 5% of all nonskin primary malignant neoplasms in dogs.1, 2 Most dogs with hemangiosarcoma are older, with a mean age of approximately 10 years (range, 3 to 15 years).1-4 German Shepherd Dogs, Golden Retrievers, Labrador Retrievers, and Standard Poodles may be overrepresented. There is not a consistent sex predilection.2, 5

In dogs, the primary site of hemangiosarcoma is typically the spleen, although other sites reported include the right atrium, dermis, subcutis, liver, lungs, kidneys, oral cavity, muscles, bones, urinary bladder, and peritoneum.1 Hemangiosarcoma typically metastasizes rapidly to the liver, omentum, mesentery, and lungs via hematogenous routes or transabdominal transplantation. Approximately two thirds of dogs with hemangiosarcoma will have evidence of metastases during necropsy.5 In reports5, 6 of dogs with splenic hemangiosarcoma, it was found during necropsy that 6 of 25 (24%) had right atrial involvement, 12 of 85 (14%) had metastasis to the brain, and 10 of 16 (62.5%) had metastases within the abdominal cavity (liver, omentum, or mesentery). Of the 12 dogs that had metastasis to the brain, 6 were examined because of primary neurologic abnormalities, which is a relatively uncommon primary finding for dogs with hemangiosarcoma.6

Staging of hemangiosarcoma has been established. Dogs that are classified as stage I have a primary tumor only, whereas dogs classified as stage II have a primary tumor with splenic rupture or lymph node involvement, and dogs classified as stage III have a primary tumor with splenic rupture or lymph node involvement and evidence of distant metastasis.8 No statistical differences in survival time have been detected among dogs with various stages of hemangiosarcoma.4

Clinical signs commonly associated with hemangiosarcoma are primarily related to anemia and can

ABBREVIATIONS

<table>
<thead>
<tr>
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<th>Definition</th>
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<tr>
<td>TS</td>
<td>Total solids</td>
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<td>pRBCs</td>
<td>Packed RBCs</td>
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include weakness, abdominal distention, tachycardia, tachypnea, pale mucous membranes, and weight loss. Some dogs may have an episode of weakness and recover within 1 or 2 days, whereas some dogs will die suddenly as a result of exsanguination when a primary tumor ruptures or as a complication of metastatic disease, disseminated intravascular coagulation, or cardiac arrhythmias. Dogs with cardiac involvement often develop pericardial effusion.\textsuperscript{8} Histologic studies\textsuperscript{3,4,9,10} report the two-thirds rule in regard to the prevalence of splenic hemangiosarcoma in a mixed clinical population of dogs. In 1 study\textsuperscript{3} in which 100 spleens were submitted for histologic examination, 66 (66%) dogs had a neoplastic lesion and 34 (34%) had a nonneoplastic lesion. Of the dogs with neoplasia, 43 of 66 (65.1%) had hemangiosarcoma, which resulted in an overall prevalence of 43%. This led to the two-thirds–two-thirds rule (ie, approx two thirds of dogs with a splenic mass will have malignant neoplasia, and two thirds of those dogs with malignant neoplasia will have hemangiosarcoma). In another report\textsuperscript{7} of 500 spleens submitted for histologic examination, 257 of 500 (51.4%) were classified as nonneoplastic, 241 (48.2%) were classified as neoplastic, and 2 (0.4%) were unclassified. Of the splenic neoplasms, hemangiosarcoma represented 122 of 241 (50.6%) submissions. Overall, hemangiosarcoma accounted for 122 of 500 (24.4%) submissions. This led to the fifty-fifty rule (ie, approx 50% of splenic masses are neoplastic and approx 50% of those will be hemangiosarcomas). Similar results have been reported in another study.\textsuperscript{10} Therefore, the prevalence of splenic hemangiosarcoma reported in the veterinary literature\textsuperscript{1,3,4,9,10} is approximately 22% to 43% of all splenic masses submitted for histologic examination. However, investigators in those studies did not correlate results with clinical signs of all dogs, including hemoperitoneum, and results may not be applicable to other clinical populations of dogs. The prevalence of hemangiosarcoma in anemic dogs with a splenic mass and hemoperitoneum requiring a transfusion is an area of debate among veterinarians.

Unfortunately, there currently is no definitive method to diagnose hemangiosarcoma other than histologic examination because splenic hematomas are grossly indistinguishable from hemangiosarcomas, even during surgery. Clinicopathologic findings such as regenerative anemia, hypoproteinemia, thrombocytopenia, a mature neutrophilic leukocytosis, or schistocytes are supportive of but not definitively diagnostic for hemangiosarcoma and have many other causes.\textsuperscript{3,11-14} Also, a splenic mass may often times not be visible during examination of abdominal radiographs because of ascites (blood). Sectional imaging techniques, such as abdominal ultrasonography, computed tomography, or magnetic resonance imaging, may be useful in establishing a diagnosis because there are differences in imaging characteristics between malignant and nonmalignant masses.\textsuperscript{15-17} However, these imaging modalities are not always readily available, which may force owners to make the decision to proceed with stabilization and surgery in the face of an uncertain outcome. Having the ability to inform owners of the prevalence of hemangiosarcoma in relation to clinical signs as well as discussing the prognosis can allow owners to be informed when making their decision to treat their dogs and to be better prepared for the results of histologic examinations. The purpose of the study reported here was to determine the prevalence of splenic hemangiosarcoma in a specific population of dogs and to determine whether results of any readily available point-of-care testing (ie, PCV, concentration of T5, and platelet count) could help distinguish between dogs with hemangiosarcoma and dogs with lesions other than hemangiosarcoma at time of admission to a hospital.

**Materials and Methods**

**Case selection**—Blood bank logs from January 1, 2003, to December 31, 2005 were reviewed to identify all dogs that received pRBCs during treatment for hemoperitoneum or a splenic mass at Angell Animal Medical Center, Boston, Mass. Inclusion and exclusion criteria were chosen to ensure severity of illness. This revealed 191 dogs that received 237 transfusions. Of the 191 dogs that received transfusions, those that had clinical signs of anemia (tachycardia, tachypnea, pale mucous membranes, or hyperdynamic pulses), had been splenectomized, and had definitive splenic pathologic changes during histologic examination were included in the study. Exclusion criteria included dogs with a history of trauma or a substantial increase in coagulation times (> 33% above the upper limit of the reference range), dogs that received only medical management, dogs that did not have a splenic mass at the time of surgery, and dogs with no histologic examination results. Dogs that had a bleeding episode from presumed metastatic lesions associated with a prior diagnosis of hemangiosarcoma and dogs that were euthanized were also excluded. Finally, dogs that had incidental splenic disease and dogs that were not sufficiently anemic to warrant transfusion for their splenic disease were also excluded.

**Medical records review**—Data obtained from the medical records included age, breed, sex, body weight, technique used to diagnose hemoperitoneum (via abdominocentesis or ultrasonography [or both]), PCV, T5 concentration, and platelet counts at the time of admission to the hospital as well as the total volume of pRBCs transfused and number of days in the hospital. Results of thoracic radiography, evaluation of surgery reports, and histologic examination of splenic specimens were also assessed. Survival times were recorded when available. Medical records were reviewed to ensure dogs did not have a substantial increase in coagulation times or a history of trauma. Potential predictive factors investigated for hemangiosarcoma included body weight, age, sex, PCV, T5 concentration, and platelet counts obtained at the time of admission to the hospital; total volume of pRBCs transfused; and number of days in the hospital.

**Statistical analysis**—Data were grouped, and the mean, median, SD, and range for all variables were calculated by use of a statistical software program.\textsuperscript{4} Dogs with hemangiosarcoma and dogs with lesions other than hemangiosarcoma did not differ significantly with
The overall prevalence of hemangiosarcoma independent of hemoperitoneum was 51 of 89 (57.3%) dogs, compared with 50 of 71 (70.4%) dogs with hemangiosarcoma and hemoperitoneum (Figure 2). For the remainder of the statistical analysis, only the 71 dogs with hemoperitoneum were included.

At the time of admission to the hospital, mean PCV was 27.9% (median, 28%; range, 13% to 47%), mean TS concentration was 5.96 mg/dL (median, 6.0 mg/dL; range, 3.8 to 9.2 mg/dL), and mean platelet count was 112,800 cells (median, 112,840 cells; range, 23,000 to 301,000 cells) for all 71 dogs. For 50 dogs with hemangiosarcoma, mean PCV was 27.2% (median, 27%; range, 13% to 47%), mean TS concentration was 5.78 mg/dL (median, 5.8 mg/dL; range, 3.8 to 8.5 mg/dL), and mean platelet count was 99,900 cells (median, 99,880 cells; range, 23,000 to 300,000 cells) at time of admission. For dogs with other splenic lesions, mean PCV was 29.8% (median, 30%; range, 20% to 38%), mean TS concentration was 6.40 mg/dL (median, 6.4 mg/dL; range, 4.6 to 9.2 mg/dL), and mean platelet count was 145,200 cells (median, 145,200 cells; range, 50,000 to 301,000 cells) at time of admission. Five dogs with hemangiosarcoma and 3 dogs with lesions other than hemangiosarcoma did not have recorded platelet counts at time of admission because of cancellation of the test as a result of euthanasia, cardiac arrest, or financial concerns. Dogs with splenic hemangiosarcoma were identified as having significantly lower TS concentrations (P = 0.024) and platelet counts (P = 0.008) at time of admission to the hospital. However, PCV at time of admission did not differ significantly (P = 0.064) between the 2 groups. A Fisher exact test revealed a significant (P = 0.009) difference between dogs with hemangiosarcoma and dogs with other splenic lesions, 12 were male (10 castrated and 2 sexually intact). Of the 21 dogs with a splenic mass, clinical signs of anemia, and hemoperitoneum with hemangiosarcoma in the study, 27 were male (25 castrated and 2 sexually intact) and 1 (1.4%) was a sexually intact female. Of the 50 dogs with hemangiosarcoma in the study, 35 (49.3%) were castrated males, 4 (5.6%) were sexually intact males, 31 (43.7%) were spayed females, and 1 (1.4%) was a sexually intact female. Of the 50 dogs with hemangiosarcoma in the study, 27 were male (25 castrated and 2 sexually intact) and 23 were female (22 spayed and 1 sexually intact). Of the 21 dogs with other splenic lesions, 12 were male (10 castrated and 2 sexually intact) and 9 were spayed females. Mean body weight of dogs in the study was 33.3 kg (73.3 lb), with a range of 5.4 to 36.1 kg (11.9 to 123.4 lb), and it did not differ significantly between groups.

Of the 71 dogs included in the study, 54 (76.1%) had malignant splenic neoplasia and 17 (23.9%) had a benign splenic lesion (Figure 1). Of the 54 dogs with malignant splenic neoplasia, 50 (92.6%) had hemangiosarcoma. Overall, 50 of 71 (70.4%) dogs in the study had splenic hemangiosarcoma, 4 (5.6%) had another form of malignant splenic neoplasia (metastatic carcinoma [n = 1], poorly differentiated sarcoma [2], and lymphoma [1]), and 17 (23.9%) had benign splenic masses (nodular hyperplasia [10] and hematoma [7]).

Eighteen dogs were excluded because they did not have hemoperitoneum. However, these dogs were included explicitly to assess the association that hemoperitoneum had with hemangiosarcoma in these dogs with clinical signs of anemia and a splenic mass. Only 1 of these 18 (5.5%) dogs had splenic hemangiosarcoma.
and dogs with lesions other than hemangiosarcoma at the time of admission when a cutoff value of < 5.8 mg/dL was used for the TS concentration. In addition, a cutoff value of < 5.8 mg/dL for the TS concentration yielded a positive predictive value for hemangiosarcoma of 87.1% but a negative predictive value of hemangiosarcoma of only 42.5% (Figure 3). A Fisher exact test also revealed a significant (P = 0.004) difference between dogs with hemangiosarcoma and dogs with lesions other than hemangiosarcoma when a cutoff value of <90,000 cells was used for the platelet count at time of admission. A cutoff value of <90,000 cells for the platelet count yielded a positive predictive value for hemangiosarcoma of 92.0% but a negative predictive value for hemangiosarcoma of only 42.1% (Figure 4). A liver biopsy specimen was obtained in 46 of 50 dogs with splenic hemangiosarcoma. Twenty-nine of 46 (63.0%) dogs with splenic hemangiosarcoma did not have evidence of hemangiosarcoma in a liver biopsy specimen, whereas 17 (37.0%) did.

All dogs received a mean of 14.16 mL of pRBCs/kg (6.44 mL of pRBCs/lb), with a median of 11.44 mL/kg (5.20 mL/lb) and a range of 5.83 to 47.80 mL/kg (2.65 to 21.73 mL/lb). Dogs with hemangiosarcoma received a mean of 15.19 mL of pRBCs/kg (6.90 mL of pRBCs/lb), with a median of 11.51 mL/kg (5.23 mL/lb) and a range of 6.36 to 47.80 mL/kg (2.89 to 21.73 mL/lb). Dogs with hemangiosarcoma were hospitalized for a mean of 2.90 days (median, 3 days; range, 1 to 5 days). Dogs with hemangiosarcoma were hospitalized for a mean of 2.95 days (median, 3 days; range, 2 to 5 days), and dogs with lesions other than hemangiosarcoma were hospitalized for a mean of 2.84 days (median, 3 days; range, 1 to 4 days). Number of days in the hospital and, therefore, associated cost to an owner did not differ significantly (P = 0.070) between the groups.

Of the 50 dogs with splenic hemangiosarcoma, 28 had a recorded outcome. Three dogs had cardiopulmonary arrest and died during hospitalization, 1 dog was euthanized during surgery because of diffuse metastatic disease, 1 dog was euthanized immediately after surgery, and 1 dog was euthanized the day after surgery because of clinical deterioration and financial concerns. Of the 48 dogs discharged from the hospital, 22 were available for follow-up evaluation. One dog with metastatic disease had a recurrence of hemoperitoneum 2 months later, and 1 dog died before arrival at the hospital 3 months later, presumably as a result of bleeding metastatic lesions. Twenty dogs were euthanized at the request of the owners because of recurrence of clinical signs. Mean survival time was 77.4 days (median, 57 days; range, 1 to 303 days) after discharge from the hospital.

Discussion

Hemoperitoneum is an emergency commonly encountered in veterinary medicine. When there is no history of trauma or coagulopathy, it is a concern that most dogs will have a ruptured splenic mass and hemangiosarcoma with its associated poor prognosis. Histologic studies have revealed a prevalence of splenic hemangiosarcoma between 22% and 43%. These studies were often conducted on specimens submitted to large histopathology laboratories; they do not comprise a consistent clinical population, and results are not applicable to the clinical population investigated in the study reported here. To the authors' knowledge, there is 1 study in which investigators correlate clinical signs and hematologic abnormalities with histopathologic findings in dogs with nontraumatic hemoperitoneum. In that study, there was a definitive diagnosis for 30 dogs obtained by use of histologic examination or necropsy. Twenty-four of the 30 (80%) dogs had malignant neoplasia. Hemangiosarcoma accounted for 21 of 24 (88%) malignancies and 21 of all 30 (70%) diagnosed conditions. A splenic mass was not a criterion for inclusion, and transfusion requirements...
were not discussed. Furthermore, only 12 dogs in that study had a splenic mass as the source of bleeding at the time of surgery. In addition, investigators in that study determined that clinicopathologic abnormalities were similar for all dogs, regardless of the cause for the abdominal bleeding. Other reports represent a combination of dogs and range from incidental discovery of splenic disease to dogs that were in shock and critically ill with hemoperitoneum as a result of splenic disease. Some of the histopathologic studies have included dogs with systemic splenomegaly attributable to venous congestion, splenic torsion, infarction, myeloid metaplasia, and lymphoid hyperplasia.

It is widely accepted that dogs with a splenic mass and hemoperitoneum have a higher prevalence of hemangiosarcoma than dogs that have splenic masses incidentally discovered without hemoperitoneum. In 1 study, 39 of 51 (76.4%) dogs with splenic hemangiosarcoma had hemoperitoneum, whereas only 24 of 81 (29.6%) dogs with a splenic hematoma had hemoperitoneum. However, multiple, definitive, clinical studies in which investigators have determined the prevalence of hemangiosarcoma in dogs with hemoperitoneum are lacking. Hemangiosarcoma has a poor prognosis for long-term survival, and there is currently no technique to definitively diagnose hemangiosarcoma before histologic examination. Therefore, owners need to be informed about the chances that their dogs have hemangiosarcoma and the implications for the future of their pets.

The goal of the study reported here was to determine the prevalence of hemangiosarcoma in a consistent population of dogs and to examine factors at the time of admission that may have been linked to hemangiosarcoma. Dogs chosen had a splenic mass and nontraumatic hemoperitoneum and were anemic to the point that they needed a transfusion. This population was chosen because it is often the owners of these dogs who need to quickly make decisions regarding stabilization, treatment, and surgery, sometimes without the availability of ultrasonographic findings or results of complete hematologic examinations that could raise the clinical suspicion of hemangiosarcoma. Veterinarians are obligated to ensure that owners of these dogs are informed about the prevalence of hemangiosarcoma, treatment options, and the overall poor prognosis associated with hemangiosarcoma before committing to treatment.

As mentioned previously, the signalment of dogs in the study reported here was similar to that in other reports for medium- to large-breed older dogs of both sexes. Because they are common breeds in the general population, it is difficult to conclude whether these breeds were overrepresented, and we did not compare our numbers to those of a control population. Initial clinical signs were vague and included weakness, lethargy, anorexia, reluctance to walk, and collapse. All dogs were anemic to the point that they had clinical signs and required a transfusion with at least 1 unit of PCVs.

The prevalence of splenic hemangiosarcoma was 70.4% (50/71 dogs) in the study reported here. Hemoperitoneum was strongly associated with the diagnosis of splenic hemangiosarcoma in this study, which was similar to results in other studies. As described in the criteria for case selection, 18 dogs were excluded from analysis because they did not have hemoperitoneum. It is interesting that only 1 of these 18 dogs had splenic hemangiosarcoma. Thus, the overall prevalence of hemangiosarcoma independent of hemoperitoneum was 57.3% (51/89 dogs).

The prevalence of hemangiosarcoma in the study reported here was higher than that in most histopathologic studies and likely represented the consistent severity of illness for which we purposefully selected. The prevalence of 70.42% for hemangiosarcoma in our study may have actually underestimated the true prevalence because it did not account for dogs that died at home, were euthanized in the examination room because of a poor prognosis or financial concerns, were euthanized during surgery because of gross metastatic disease with no submission for histologic examination, or did not undergo surgery because of coagulopathies or signs of metastatic disease evident during examination of thoracic radiographs or abdominal ultrasonograms. Frequently, only 1 or 2 of the histologic sections are diagnostic, especially in dogs with hemangiosarcoma in which other sections have extensive areas of hemorrhage and necrosis. Therefore, when the entire spleen is not examined, a small pocket of neoplastic cells may be missed. Additional tissue sections should always be requested when hemangiosarcoma is highly suspected but not initially diagnosed. Furthermore, by excluding dogs with substantial increases in coagulation times to ensure dogs with primary coagulopathies or rodenticide intoxication were not included, we may have excluded dogs with disseminated intravascular coagulation, which is a known condition in dogs with hemangiosarcoma.

Three factors were associated with hemangiosarcoma in our study. First, hemoperitoneum was strongly associated with splenic hemangiosarcoma. Second, the TS concentrations and platelet counts of dogs with hemangiosarcoma were significantly lower at time of admission to the hospital. Furthermore, when a value of < 5.8 mg/dL was chosen for a cutoff value for the TS concentration, a positive predictive value of 87.1% and a negative predictive value of 42.5% were calculated for hemangiosarcoma. When a value of < 90,000 cells was chosen as a cutoff value for the platelet count at the time of admission, a positive predictive value of 92.0% and a negative predictive value of 42.1% were calculated for hemangiosarcoma. Although these numbers differed significantly, a lower TS concentration or platelet count (or both) is likely more representative of severe hemorrhage rather than a true biomarker for predicting hemangiosarcoma. On the other hand, hemangiosarcoma is an invasive tumor arising from the vascular endothelium, and hemorrhage associated with hemangiosarcoma may be more severe, which would account for the lower TS concentrations and platelet counts at the time of admission to the hospital.

A liver biopsy specimen was obtained from 46 of 50 dogs, and 17 (37.0%) had histologic evidence of hemangiosarcoma. Most dogs with metastatic disease...
in the liver had gross evidence at the time of surgery. It is important to mention that some dogs with liver nodules at the time of surgery had benign hepatic hyperplastic nodules and that euthanasia at the time of surgery should not always be recommended to owners solely on the basis of liver nodules. This raises the issue of whether to biopsy the liver in these dogs. Reasons not to biopsy include risk of hemorrhage, surgical stability and duration of surgery, financial considerations, owner preference, and surgeon preference when organs appear grossly normal.

Survival duration in the study (when available) was poor and similar to that in other reports. Median survival time for dogs with hemangiosarcoma after splenectomy alone is 86 days, with < 10% surviving for 1 year.1,19 However, dogs that receive doxorubicin-based chemotherapy after splenectomy have longer median survival times. Dogs that received chemotherapy after splenectomy had a median survival time of 172 days.1,19 In addition, dogs with solitary or incidental splenic masses appear to do better, whereas survival has not been significantly or consistently affected by tumor size or gross metastatic disease.2-5 Staging and the effects of chemotherapy were not directly evaluated in the study reported here.

Future investigations into the prevalence of hemangiosarcoma in dogs could include the evaluation of dogs that have a splenic mass and are anemic but that do not have hemoperitoneum or dogs that have incidentally discovered splenic masses. Dogs in the latter category likely have a lower prevalence of splenic hemangiosarcoma. In the future, molecular markers of malignancy may be available that could increase the likelihood of a definitive diagnosis without the morbidity and mortality rates associated with surgery.

Weaknesses of the study reported here included the small number of dogs and problems inherent in retrospective studies, such as inconsistent or incomplete records, differences in treatment and stabilization among dogs, and lack of definitive follow-up monitoring because of the nature of the hospital as an emergency and referral institution. In addition, we were unable to compare lactate concentrations at the time of admission between groups of dogs. Approximately a third of the dogs in this study had a lactate concentration recorded for the time of admission. Although it subjectively appeared that the lactate values were higher in the hemangiosarcoma group, insufficient numbers prohibited full analysis of this association.

Analysis of results of the study reported here suggested that anemic dogs with clinical signs, a splenic mass, and hemoperitoneum that required a transfusion without a history of trauma or coagulopathy had a 76.1% chance of having malignant neoplasia and a 70.4% chance of having hemangiosarcoma. In addition, dogs with hemangiosarcoma had significantly lower TS concentrations and platelet counts at the time of admission, compared with values for dogs with similar clinical signs but other splenic lesions. Additionally, detection of hemoperitoneum should raise the index of suspicion for hemangiosarcoma. Owners need to be informed about the prevalence of hemangiosarcoma and the associated financial costs, treatment options, and poor prognosis.

References